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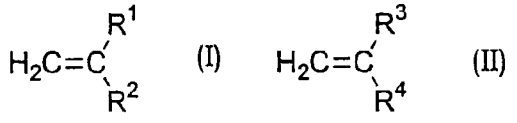
(54) Title: POLYMER AND ITS USE



(57) Abstract: A polymer or its salt which is obtainable by polymerization of a monomer of the formula (I) or its salt in the presence of a radical initiator, or by polymerization of a monomer of the formula (I) or its salt with a monomer of the formula (II) or its salt in a molar ratio of (I): (II) being 1:0.1 to 1:25 in the presence of a radical initiatorwherein R1 and R3 are each hydrogen atom or lower alkyl group, R2 and R4 are each acyl group,aliphatic silyl group,amino lower alkyl group which may have one or more suitable substituent(s),heterocyclic group which may have one or more suitable substituent(s) orcarboxy group esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl.

DESCRIPTION

POLYMER AND ITS USE

TECHNICAL FIELD

This invention relates to a kind of novel polymers having ability for adsorbing phosphate, to a pharmaceutical composition containing the same and to their use as a medicament.

BACKGROUND ART

Renal insufficient patients have difficulties in excretion of phosphate to urine. Accumulated phosphate in the patient causes central and peripheral neuropathy, cardiomyopathy, hyperlipidemia, glycometabolism disorder, pruritus, anemia, hypogonadism, disorder for diffusing of the lung, arteriosclerosis, immunodeficiency, renal failure, etc. (Jin to Touseki, 37, 2: 3211994). Even during dialysis, those pathemas and complications cannot be dissolved. Therefore, it is essential for the renal insufficient patients to treat hyperphosphoremia. Currently, dietotherapy and/or administration of a peroral phosphate adsorbent are applied for treating hyperphosphoremia. However, the dietotherapy is not effective for decreasing the amount of phosphate in the blood because it is inevitable for the patient to have some amount of proteins in the ingesta.

As the peroral phosphate adsorbents, aluminum preparation (e.g., aluminum hydroxide), calcium preparation (e.g., calcium carbonate, calcium acetate), magnesium preparation (e.g., magnesium carbonate) and anion-exchange resins (e.g., Rena Gel®, manufactured by Chugai Pharmaceutical Co., Ltd. and Kirin Brewery Company, Limited) are used.

Among these phosphate adsorbents, the aluminum preparation, calcium preparation and magnesium preparation are adsorbed through the intestine and tend to accumulate in the body, and the anion-exchange resins tend to cause side effects such as constipation, diarrhea, flatus, nausea, emesis, etc. And further, the dose of the anion-exchange resins is so large due to low ability of adsorption that

intensifies such side effects.

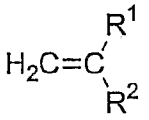
DISCLOSURE OF INVENTION

Accordingly, an object of this invention is to provide a kind of novel polymers having ability for adsorbing phosphate. Since the polymer of the present invention has stronger ability of adsorption, the dosage of the polymer can be reduced.

Another object of this invention is to provide a pharmaceutical composition containing a polymer as an active ingredient.

Further object of this invention is to provide a use of the polymers for treating or preventing hyperphosphoremia.

The novel polymers of this invention have ability for adsorbing phosphate and can be obtained by polymerization of a monomer of the formula (I) or its salt in the presence of a radical initiator, or by polymerization of a monomer of the formula (I) or its salt with a monomer of the formula (II) or its salt in a molar ratio of (I) : (II) being 1:0.1 to 1:25 in the presence of a radical initiator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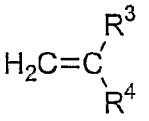

(II)

wherein

R^1 and R^3 are each hydrogen atom or lower alkyl group,

R^2 and R^4 are each acyl group,

aliphatic silyl group,

amino lower alkyl group which may have one or more suitable substituent(s),

heterocyclic group which may have one or more suitable substituent(s) or

carboxy group which may be esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl.

In the above and subsequent descriptions of the present specification and claims, suitable examples and illustrations of the various definitions which the present invention includes within the scope are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise indicated.

Examples of "one or more" are the numbers of 1 to 6, in which the preferred one is the number of 1 to 3, and the most preferred one is the number of 1 or 2.

Preferred examples of "halogen" are fluorine, chlorine, bromine, iodine and the like.

Preferred examples of "lower alkoxy" moiety include straight or branched ones such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neo-pentyloxy, hexyloxy, isohexyloxy or the like.

Preferred examples of "lower alkyl" moiety include straight or branched ones having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl or the like.

Preferred examples of "aryl" and "ar" moiety include phenyl which may have lower alkyl (e.g., phenyl, mesityl, xylyl or tolyl), naphthyl, anthryl, indanyl, fluorenyl or the like, and this "aryl" and "ar" moiety may have one or more halogen.

Preferred examples of "aroyl" include benzoyl, toluoyl, naphthoyl, anthrylcarbonyl and the like.

Preferred examples of "heterocyclic group" or "heterocyclic" moiety include :

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic groups containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl or 2H-1,2,3-triazolyl), and tetrazolyl (e.g., 1H-tetrazolyl or 2H-tetrazolyl);

saturated 3- to 8-membered (more preferably 5- or 6-membered)

heteromonocyclic groups containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl and azetidinyl;
unsaturated condensed heterocyclic groups containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isozuinolyl, indazolyl and benzotriazolyl;
unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic groups containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl and oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl or 1,2,5-oxadiazolyl);
saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic groups containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl and morpholino;
unsaturated condensed heterocyclic groups containing 1 or 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl and benzoxadiazolyl;
unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic groups containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl or 1,2,5-thiadiazolyl) and dihydrothiazinyl;
saturated 3- to 8-membered (more preferebly 5- or 6-membered) heteromonocyclic groups containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example thiazolidinyl, thiomorpholinyl and thiomorpholino;
unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic groups containing 1 or 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl and dihydrodithionyl;
unsaturated condensed heterocyclic groups containing 1 or 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl and imidazothiadiazolyl;
unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic groups containing an oxygen atom, for example furyl;
saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic groups containing 1 or 2 oxygen atom(s), for example, tetrahydrofuran, tetrahydropyran, dioxacyclopentane and

dioxacyclohexane;
unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic groups containing an oxygen atom and 1 ot 2 sulfur atom(s), for example, dihydrooxathiinyl;
unsaturated condensed heterocyclic groups containing 1 or 2 sulfur atom(s), for example, benzothienyl and benzodithiinyl;
unsaturated condensed heterocyclic group containing an oxygen atom and 1 or 2 sulfur atom(s), for example, benzoxathiinyl; and the like, and this "heterocyclic group" may have one or more suitable substituent(s) selected from the group consisting of sulfo, lower alkyl, oxo, halogen and hydroxy.

Preferred examples of "acyl group" include aliphatic acyl, aromatic acyl, arylaliphatic aciyl and heterocyclic-aliphatic acyl derived from carboxylic acid, carbonic acid, carbamic acid and sulfonic acid.

More preferred examples of the "acyl group" are illustrated as follows:

carboxy; carbamoyl; mono or di(lower)alkylcarbamoyl (e.g., methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, propylcarbamoyl, n-butylcarbamoyl or 1,1-dimethylcarbamoyl);

aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl or icosanoyl);
lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, n-butoxycarbonyl, tert-butoxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl or heptyloxycarbonyl);
lower alkenyloxycarbonyl (e.g., vinyloxycarbonyl, propenyloxycarbonyl, allyloxycarbonyl, butenyloxycarbonyl, butedienyloxycarbonyl, pentenyloxycarbonyl or hexenyloxycarbonyl);
lower or higher alkylsulfonyl (e.g., methylsulfonyl or ethylsulfonyl);
lower or higher alkoxysulfonyl (e.g., methoxysulfonyl or ethoxysulfonyl);
aromatic acyl such as aroyl (e.g., benzoyl, toluoly or naphthoyl);

ar(lower)alkanoyl [e.g., phenyl(C_1-C_6)alkanoyl (e.g., phenylacethyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl or phenylhexanoyl), or naphthyl(C_1-C_6)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl or naphthylbutanoyl)];

ar(lower)alkenoyl [e.g., phenyl(C_3-C_6)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentanoyl or phenylhexenoyl), or naphthyl(C_3-C_6)alkenoyl (e.g., naphthylpropenoyl or naphthylbutenoyl)];

ar(lower)alkoxycarbonyl [e.g., phenyl(C_1-C_6)alkoxycarbonyl (e.g., benzyloxycarbonyl), or fluorenyl(C_1-C_6)alkoxycarbonyl (e.g., fluorenylmethyloxycarbonyl)];

aryloxycarbonyl (e.g., phenoxycarbonyl or naphthyloxycarbonyl);

aryloxy(lower)alkanoyl (e.g., phenoxyacetyl or phenoxypropionyl);

arylcarbamoyl (e.g., phenylcarbamoyl);

arylthiocarbamoyl (e.g., phenylthiocarbamoyl);

arylglyoxyloxy (e.g., phenylglyoxyloyl or naphthylglyoxyloyl);

arylsulfonyl which may have 1 to 4 lower alkyl (e.g., phenylsulfonyl or p-tolylsulfonyl);

aroyl (e.g., benzoyl) substituted with one or more suitable substituent(s);

heterocyclic aryl such as heterocycliccarbonyl;

heterocyclicoxycarbonyl;

heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl or heterocyclichexanoyl);

heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl or heterocyclichexenoyl);

heterocyclicglyoxyloyl; and the like,

in which suitable "heterocyclic" moieties in the terms "heterocycliccarbonyl", "heterocyclicoxycarbonyl", "heterocyclic(lower)alkanoyl", "heterocyclic(lower)alkenoyl" and "heterocyclicglyoxyloyl" can be referred to aforementioned "heterocyclic" moieties.

Preferred examples of the lower alkyl group for R^1 and R^3 are referred to aforementioned "lower alkyl", in which the more preferred

ones are methyl, ethyl, propyl, n-butyl, t-butyl, pentyl and n-hexyl.

Preferred examples of the acyl group for R^2 and R^4 can be referred to aforementioned "acyl group", in which the more preferred ones are lower alkylcarbamoyl group such as methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, n-butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl and 1,1-dimethylethylcarbamoyl;
arylcarbamoyl group such as phenylcarbamoyl and naphthylcarbamoyl;
lower alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, n-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl;
aforementioned heterocyclicoxycarbonyl group, in which the preferred ones are quinolinyloxycarbonyl, pyridyloxycarbonyl and furyloxycarbonyl; and
aforementioned heterocycliccarbonyl group, in which the oreferred ones are morpholinylcarbonyl, pyridylcarbonyl, furoyl, thenoyl and imidazoylcarbonyl.

Preferred examples of the aliphatic silyl group for R^2 and R^4 are trimethylsilyl and triethylsilyl.

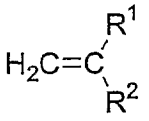
Preferred examples of the amino(lower)alkyl group for R^2 and R^4 are aminomethyl, aminoethyl, aminopropyl, amino-n-butyl, aminopentyl and aminohexyl.

Preferred examples for the heterocyclic group for R^2 and R^4 can be referred to aforementioned "heterocyclic group", in which the more preferred ones are pyridyl, thienyl, furyl, pyrolyl, thiazolyl, oxazolyl, isoxazolyl and quinolyl.

The above lower alkylcarbamoyl group, arylcarbamoyl group, lower alkoxycarbonyl group, heterocyclicoxycarbonyl group, heterocycliccarbonyl group, amino(lower)alkyl group and heterocyclic group may have one or more substituent(s) selected from the group consisting of sulfo; hydroxy; carboxy; amino; sulfo(lower)alkyl-di(lower)alkylamino such as sulfopropyl-dimethylamino, sulfomethyl-dimethylamino and sulfoethyl-dimethylamino;
carboxy(lower)alkylamino such as carboxymethyl-dimethylamino;

dihydroxyboraneyl; tri(lower alkyl)ammonium such as trimethylammonium; glycosyloxy; heterocyclic carbonylamino such as (2-oxo-1,2-dihydro-4-pyrimidinyl)carbonylamino, (2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)carbonylamino and (5-fluoro-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)carbonylamino; heterocyclic(lower)alkylaminocarbonylamino such as 2-(1H-imidazol-5-yl)ethylaminocarbonylamino; -(lower alkoxy)$_8$-lower alkoxy such as -$(OCH_2CH_2)_8$-OCH_3 ;and halogen such as chlorine and bromine.

The preferred polymer of the invention can be obtained by polymerization of a monomer of the formula (I) or its salt in the presence of a radical initiator, or by polymerization of a monomer of the formula (I) or its salt with a monomer of the formula (II) or its salt in a molar ratio of (I) : (II) being 1:0.1 to 1:25, preferably 1:0.5 to 1:20 in the presence of a radical initiator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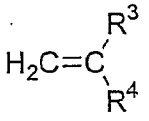

(II)

wherein

R^1 and R^3 are each as defined in the above, and

R^2 and R^4 are each

lower alkyl carbamoyl group, aryl carbamoyl group, lower alkoxycarbonyl group, heterocyclicoxycarbonyl group or heterocyclccarbonyl group, each of which may have one or more suitable substituent(s);

tri(lower)alkylsilyl group;

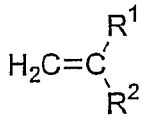
amino lower alkyl group which may have one or more suitable substituent(s);

heterocyclic group which may have one or more suitable substituent(s); or

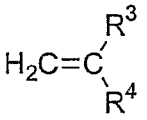
carboxy group which may be esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower

alkenoyl.

The more preferred polymer of the invention can be obtained by polymerization of a monomer of the formula (I) or its salt in the presence of a radical initiator, or by polymerization of a monomer of the formula (I) or its salt with a monomer of the formula (II) or its salt in a molar ratio of (I) : (II) being 1:0.1 to 1:25, preferably 1:0.5 to 1:20 in the presence of a radical initiator



(I)



(II)

wherein

R^1 and R^3 are each as defined in the above, and

R^2 and R^4 are each

lower alkyl carbamoyl group which may have one or more substituents selected from the group consisting of sulfo, hydroxy, carboxy, amino, sulfo(lower)alkylamino and carboxy(lower)alkylamino, or

lower alkoxycarbonyl group which may have one or more substituents selected from the group consisting of hydroxy, amino, lower alkylamino, glycosyloxy, heterocyclic carbonylamino and heterocyclic(lower)alkylaminocarbonylamino;

tri(lower)alkylsilyl group;

amino lower alkyl group which may have one or more suitable substituent(s);

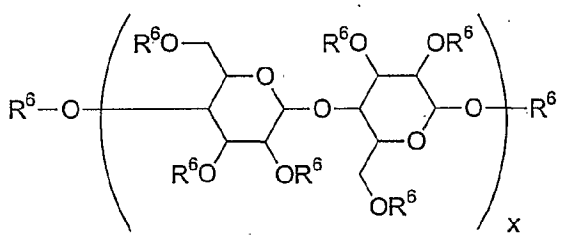
heterocyclic group which may have one or more suitable substituent(s); or

carboxy group which may be esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl.

Suitable salts of the polymers, monomers of the formula (I), the formula (Ia) and the formula (II) are conventional non-toxic salts such as salt with an alkali metal [e.g., lithium, sodium or potassium] and an alkaline earth metal [e.g., calcium or magnesium], ammonia, an

organic base [e.g., trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine or N,N'-dibenzylethylenediamine], an organic acid [e.g., formic acid, acetic acid, trifluoroacetic acid, maleic acid, tartaric acid, oxalic acid, methanesulfonic acid, benzenesulfonic acid or toluenesulfonic acid], an inorganic acid [e.g., hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid], an amino acid [e.g., arginine, aspartic acid or glutamic acid] or the like.

The preferred monomers of the formula (I) and the formula (II) are 2-glucosylethyl methacrylate (GEMA), N-tris(hydroxymethyl)methylacrylamide (NAT), methylcellulose acrylate (MCA) represented by the formula :



wherein R^6 is hydrogen, methyl or vinylcarbonyl and x is an integer of 1 or more, 2-aminoethyl methacrylate hydrochloride (AEM-HCl), allylamine hydrochloride (AL-Am-HCl), dimethylacrylamide (DMAA),acrylic acid (AA), (acryloylamino)(hydroxy)acetic acid (AHA), 4-acryloylmorpholine (AM), 2-(acryloylamino)-2-methyl-1-propanesulfonic acid (AMP), 3-(acryloylamino)phenylboronic acid (APB), [[3-(acryloylamino)propyl](dimethyl)ammonio]acetate (APDAA), 3-[[3-(acryloylamino)propyl](dimethyl)ammonio]-1-propanesulfonate (APDAP), calcium diacrylate (CDA), 5-chloro-8-quinolinyl acrylate (CQA), 2-{[(2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)carbonyl]amino}ethyl 2-methylacrylate (DCAEM), 2-{[(5-fluoro-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)carbonyl]amino}ethyl 2-methylaceylate (FCAEM), 2-(glycosyloxyl)ethyl 2-methacrylate (GEMA), N-(hydroxymethyl)acrylamide (HA), 2-{[(8-hydroxy-5-quinolinyl)carbonyl]amino}-ethyl 2-methylacrylate (HCAEM), 2-hydroxy-3-(methacryloyloxy)-N,N,N-trimethyl-1-propanaminium chloride (HMTP-HCl), 2-[({[2-(1H-imidazol-5-yl)ethyl]amino}carbonyl)amino]ethyl 2-methylacrylate (IMA), lithium

acrylate (LA), 2-methylacrylic acid (MAA), methyl 2-methylacrylate (MMA), 3,6,9,12, 15,18,21,24,27-nonaoxaoctacos-1-yl 2-methylacrylate (NM), 2-{[(2-oxo-1,2-dihydro-4-pyrimidinyl)carbonyl]amino}ethyl 2-methylacrylate (OCAEM), trimethyl(vinyl)silane (TVS) and 2-(2-vinyl-1-pyridiniumyl)ethanesulfonate (VPES).

In the above and subsequent descriptions of the present specification and claims, suitable example of "an integer of 1 or more" may be an integer of 1 to 20,000, in which the preferred one is an integer of 1 to 1,000, and more preferred one is 1 to 500, and the most preferred one is 1 to 100.

The preferred radical initiators are the ones having azo group in the molecule and the peroxides which may have perfluoroalkanoyl groups.

The peroxides having perfluoroalkanoyl groups are represented by the formula (III):

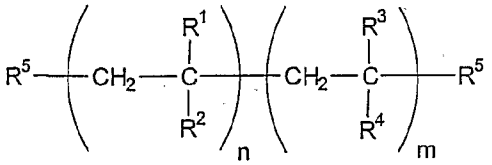
$$(R^5COO)_2 \qquad \text{(III)}$$

wherein R^5 is a perfluoro(lower)alkyl group which may have one or more suitable substituent(s) or a cycloalkyl group substituted with one or more of fluorine atom(s).

The preferred radical initiators of the formula (III) are 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoyl peroxide (PFPO-2), 2,3,3,3-tetrafluoro-2-[1,1,2,3,3,3-hexafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propoxy]propanoyl peroxide (PFPO-3), trifluoroacetyl peroxide (FAP), 2,2,3,3,4,4,4-heptafluorobutanoyl peroxide (FBP), 2,3,3,3-tetrafluoro-2-{1,1,2,3,3,3-hexafluoro-2-[1,1,2,3,3,3-hexafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propoxy]propoxy}propanoyl peroxide (PFPO-4), 2,4,4,5,7,7,8,10,10,11,13,13,14,14,15,15,15-heptadecafluoro-2,5,8,11-tetrakis(trifluoromethyl)-3,6,9,12-tetraoxapentadecan-1-oyl peroxide (PFPO-5), 1,2,2,3,3,4,4,5,5,6,6-undecafluorocyclohexanecarbonyl peroxide (CPFP) and 1,2,2,3,3,4,4,4a,5,5,6,6,7,7,8,8,8a-

heptadecafluorodecahydro-1-naphthalenecarbonyl peroxide (DPFP).

The polymers or their salts obtained by using the peroxides of the formula (III) as a radical initiator may be represented by the formula (IV) :



(IV)

wherein R^1 and R^3 are as defined in the above, and

R^2 and R^4 are as defined in the above, and

R^2 and/or R^4 may be intramolecularly and/or intermolecularly crosslinked with another R^2 or R^4,

R^5 is as defined in the above, and

n is an integer of 1 or more, and

m is an integer of 0, 1 or more.

The preferred polymers of the formula (IV) are those wherein R^1, R^3, R^5, n and m are each as defined in the above, and

R^2 and R^4 are each

lower alkyl carbamoyl group or lower alkoxycarbonyl group, each of which may have one or more suitable substituent(s),

amino lower alkyl group or

carboxy group which may be esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl, and

R^2 and/or R^4 may be intramolecularly and/or intermolecularly crosslinked with another R^2 or R^4.

The more preferred polymers (IV) are those wherein R^1, R^3, R^5, n and m are each as defined in the above, and

R^2 and R^4 are each

lower alkyl carbamoyl group which may have one or more hydroxy,

lower alkoxycarbonyl group substituted with amino or glycosyloxy,

amino lower alkyl group or

carboxy group esterified by esterified and/or etherified cellulose, and

R^2 and/or R^4 may be intramolecularly and/or intermolecularly crosslinked with another R^2 or R^4.

The polymers of the formula (IV) can be obtained by

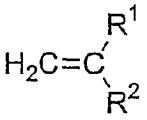
polymerization of GEMA with AEM-HCl in the presence of PFPO-2 in the molar ratio of GEMA:AEM-HCl being 1:2, 1:1, 1:0.5, 1:5 or 1:20,
polymerization of GEMA with AL-Am-HCl in the presence of PFPO-2 in the molar ratio of GEMA:AL-Am-HCl being 1:0.5,
polymerization of NAT with AEM-HCl in the presence of PFPO-2 in the molar ratio of NAT:AEM-HCl being 1:0.5,
polymerization of MCA in the presence of PFPO-2,
polymerization of MCA with AEM-HCl in the presence of PFPO-2 in the molar ratio of MCA:AEM-HCl being 1:0.6 or 1:3,
polymerization of MCA with AEM-HCl in the presence of PFPO-3 in the molar ratio of MCA:AEM-HCl being 1:3 or 1:4,
polymerization of MCA with DMAA in the presence of PFPO-2 in the molar ratio of MCA:DMAA being 1:2.6 or 1: 5.2,
polymerization of MCA with DMAA in the presence of PFPO-3 in the molar ratio of MCA:DMAA being 1:10.83,
polymerization of MCA with AL-Am-HCl in the presence of PFPO-2 in the molar ratio of MCA:AL-Am-HCl being 1:1.88 or 1:3, or
polymerization of MCA with AL-Am-HCl in the presence of PFPO-3 in the molar ratio of MCA:AL-Am-HCl being 1:4.

The examples of the radical initiators having azo group or peroxides are 2,2'-azobis(2-amidinopropane) dihydrochloride (V-50), 2,2'-diamidinyl-2,2'-azobutane dihydrochloride, 2,2'-diamidinyl-2,2'-azopentane dihydrochloride, 2,2'-bis(N-phenylamidinyl)-2,2'-azopropane dihydrochloride, 2,2'-bis(N-phenylamidinyl)-2,2'-azobutane dihydrochloride, 2,2'-bis(N,N-dimethylamidinyl)-2,2'-azopropane dihydrochloride, 2,2'-bis(N,N-dimethylamidinyl)-2,2'-azobutane dihydrochloride, 2,2'-bis(N,N-diethylamidinyl)-2,2'-azopropane dihydrochloride, 2,2'-bis(N,N-diethylamidinyl)-2,2'-azobutane dihydrochloride, 2,2'-bis(N,N-di-n-butylamidinyl)-2,2'-azopropane dihydrochloride, 2,2'-bis(N,N-di-n-butylamidinyl)-2,2'-azobutane dihydrochloride, 3,3'-bis(N,N-di-n-butylamidinyl)-3,3'-azopentane dihydrochloride, azo-bis-N,N'-dimethyleneisobutylamidine dihydrochloride, 2,2'-azobis(2,4-dimethyl-4-methoxyvaleronitrile (V-70), 2,2'-azobis(2-methylpropionitrile)(AIBN), benzoylperoxide (BPO) and m-

chloroperbenzoic acid (MCPBA).

The commercially available VA-545, VA-546, VA-548, VA-041, VA-044 and VA-046B therefor can be purchased from Wako Pure Chemical Industries Ltd. as radical initiators having azo group.

The preferred polymer or its salt of the invention is the one obtainable by polymerization of a monomer of the formula (I) or its salt in the presence of a radical initiator,



(I)

R^1 is hydrogen atom or lower alkyl group,

R^2 is lower alkyl carbamoyl group optionally substituted with one or more substituents selected from the group consisting of hydroxy, carboxy, sulfo, N,N-di(lower)alkyl-N-sulfonato(lower)alkylammonio and N,N-di(lower)alkyl-N-carboxylato(lower)alkylammonio;

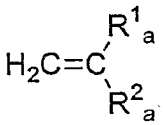
aryl group optionally substituted with dihydroxyboranyl;

lower alkoxy carbonyl group substituted with one or more substituents selected from hydroxy, ammonio and tri(lower)alkylammonio;

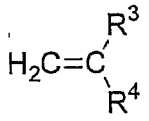
carboxy group esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl; or

pyridinium group substituted with sulfonato(lower)alkyl,

or by polymerization of a monomer of the formula (Ia) or its salt with a monomer of the formula (II) or its salt in a molar ratio of (Ia) : (II) being 1:0.1 to 1:25 in the presence of a radical initiator



(Ia)



(II)

wherein R^{1}_{a} is hydrogen atom or lower alkyl group,

R^{2}_{a} is lower alkyl carbamoyl group;

lower alkoxy carbonyl group substituted with optionally

substituted-heterocycliccarboamido,
heterocyclic(lower)alkylureido or glycosyloxy; or
heterocyclicoxycarbonyl group optionally substituted with halogen or hydroxy;

R^3 is hydrogen atom or lower alkyl group,

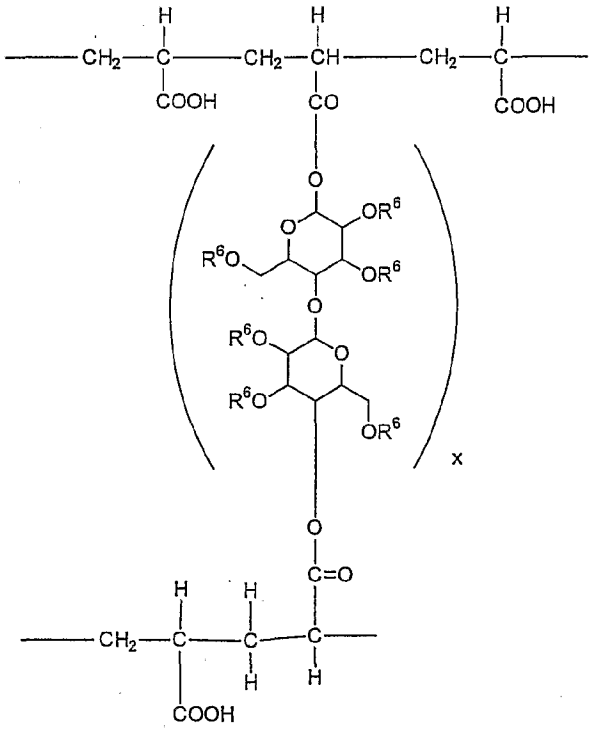
R^4 is lower alkyl carbamoyl group optionally substituted with sulfonato;
carboxy group;
lower alkoxycarbonyl group optionally substituted with lower alkoxy in which the alkyl moiety may be interrupted by oxygen atom(s);
carboxy group esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl;
amino(lower)alkyl group;
heterocyclic carbonyl group; or
tri(lower)alkylsilyl group,

provided that when $R^2{}_a$ and R^4 are the same, then $R^1{}_a$ and R^3 are different from each other.

The polymerization is usually carried out in an organic solvent such as 1,1,-dichloro-2,2,3,3,3-pentafluoropropane, 1,3-dichloro-1,2,2,3,3-pentafluoropropane or any other organic solvent which does not adversely affect the reaction, or a mixture thereof or a heterogeneous mixed solvent thereof with water.

The reaction is usually carried out in the presence of a radical initiator at a temperature under cooling to warming, preferably at the temperature of 40℃ to 50℃.

The polymer or its salt of the present invention can be intramolecularly and/or intermolecularly crosslinked by a suitable crosslinking agent or without a crosslinking agent. An example of the partial structure of the crosslinked polymer is represented by the formula :



wherein R^6 and x are each as defined in the above.

The reaction condition can be referred to the Examples mentioned below.

The polymer prepared by the above process can be isolated and purified by a conventional method such as washing with an organic solvent, pulverization, recrystallization, chromatography, reprecipitation or the like.

It is to be noted that the polymer of this invention may include one or more stereoisomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s), and all of such isomer(s) and mixture thereof are included within the scope of this invention.

It is further to be noted that isomerization or rearrangement of the polymers may occur by the effect of light, acid, base or the like, and the compounds obtained as the result of said isomerization or rearrangement are also included within the scope of the present invention.

A pharmaceutically acceptable salt of the polymer can be prepared, for example, by treating the polymer having amino group with

an appropriate acid or by treating the polymer having carboxy group with an appropriate base in accordance with a conventional method.

Also included in the scope of invention are radiolabelled derivatives of the polymer which are useful for biological studies.

The polymers and pharmaceutically acceptable salts thereof possess ability for adsorbing phosphate.

Therefore, the polymers and pharmaceutically acceptable salts thereof are useful for the treatment and/or prevention of various diseases caused by accumulated phosphates such as hyperphosphoremia.

In order to exhibit the usefulness of the present invention, the activities of the polymers are shown in the following.

In vitro phosphate binding studies

The phosphate solution (20mM Tris, 10mM Phosphoric acid) was adjusted to pH 7.0 with acetic acid. Test polymer (25mg) and the phosphate solution (20ml) were mixed, and then the mixture was shaken vigorously for an hour. Resultant solution was centrifuged for 15 minutes (15,000 rpm) with Microcon Centrifugal filter device (MILLIPORE YM-10). The phosphate concentration of the filtered solution was determined spectrophotometrically by using a standard molybdate assay (Wako P-test). The phosphate binding (%) was calculated by the formula:

$$\text{phosphate binding (\%)} = \frac{\text{Cini} - \text{Cbin}}{\text{Cini}} \times 100$$

Cini: initial concentration of the phosphate before binding,
Cbin: concentration of the phosphate after binding.

Test Results

The obtained results are shown in Table 1.

Table 1

Polymer obtained in Example	phosphate binding (%)
4	>20
5	>20
8	>20
9	>20
10	>20
13	>20
14	>20
15	>20

As shown in the above Table 1, the polymers of the present invention have superior ability for binding phosphate which indicates that they have superior ability for adsorbing phosphate.

The polymer and its salt can be administered alone or in a form of a mixture, preferably, with a calcium compound such as calcium chloride, calcium carbonate and the like. A pharmaceutical composition comprising a polymer or its salt as an active ingredient in association with a calcium compound is preferred in view point of the phosphate binding ability.

The active ingredient of this invention can be used in a form of a pharmaceutical preparation, for example, in solid or semisolid form, which contains a polymer as an active ingredient in admixture with a pharmaceutically acceptable, substantially non-toxic organic or inorganic carrier or excipient suitable for oral, parenteral such as intravenous, intramuscular, subcutaneous, intracavernous or intraarticular, external such as topical, intrarectal, transvaginal, inhalant, ophthalmic, nasal or hypoglossal applications. The active ingredient may be compounded, for example, with the conventional non-toxic, pharmaceutically acceptable carriers or excipients for ointment, cream, plaster, tablets, pellets, capsules, suppositories, emulsion, suspension, aerosols, pills, powders, syrups, injections,

troches, cataplasms, buccal tablets, sublingual tablets or any other form suitable for use.

The carriers which can be used are olive oil, wax, glucose, lactose, gum acacia, gelatin, mannitol, starch paster, magnesium trisilicate, talc, corn starch, keratin, paraffin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing the above-mentioned preparations. In addition, auxiliary, stabilizing, thickening or coloring agents and perfumes may be used. The active polymer is included in a pharmaceutical composition in an effective amount sufficient to show the desired effect.

While the therapeutically effective amount of a polymer varies depending upon the age and condition of each individual patient to be treated, in case of the systemic administration, a daily dose of about 0.01 mg-100 g, preferably 0.1 mg-50 g and more preferably 0.5 mg-10 g of the active ingredient is generally given for treating the diseases, and an average single dose of about 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 1 g, 2.5 g and 5.0 g is generally administered. Daily doses for chronic administration in humans is in the range of about 0.3 mg/body to 50 g/body.

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Example 1

2,3,3,3-tetrafluoro-2-[1,1,2,3,3,3-hexafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propoxy]propanoyl peroxide (PFPO-3, 2mmol) in 1 : 1 mixed solvents of 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-1,2,2,3,3-pentafluoropropane (200 g) was added to an aqueous solution (4.50 g) of 2-glucosylethyl methacrylate (GEMA: 6 mmol) and 2-aminoethyl methacrylate hydrochloride (AEM-HCl: 12 mmol). The heterogeneous solution was stirred vigorously at 45℃ for 5 hours under nitrogen. The obtained crude product was washed well with methanol to remove the unreacted GEMA and AEM-HCl, and dried over in vacuo at

50°C to give a polymer hydrochloride (2.63 g).

IR (KBr): 3450 (OH), 3100 (NH_3^+); 1720 (C=O), 1639 (NH_3^+), 1330(CF_3), 1243 (CF_2) cm^{-1}.

This polymer causes gelation with water and DMSO(dimethylsulfoxide). The gelation ability of this polymer was studied by measuring critical gel concentration (CGC, g/L) of this polymer in water or DMSO. CGC in water and DMSO are 123 g/L and 173 g/L, respectively.

Example 2

2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoyl peroxide (PFPO-2, 1.9 mmol) in 1 : 1 mixed solvents of 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-1,2,2,3,3-pentafluoropropane (17.71 g) was added to a mixture of a solution of AEM-HCl (0.95 g, 5.7 mmol) in water (9.0 g) and 3.31 g (5.7 mmol) of 50% aqueous solution of GEMA. After adding 100 g of the 1 : 1 mixed solvents of 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-1,2,2,3,3-pentafluoropropane, the mixture was stirred vigorously with a mechanical stirrer at 45°C for 5 hours under nitrogen. The crude product was isolated and washed well with methanol to remove the unreacted GEMA and AEM-HCl, and dried over in vacuo at 50°C for 2 days to give a polymer hydrochloride (2.68 g).

IR (KBr): 3450 (NH_3^+, OH), 1724, 1635(C=O), 1300(CF_3), 1244 (CF_2) cm^{-1}.

CGC in water and DMSO are 267 g/L and 115 g/L, respectively.

The obtained polymer causes gelation only with water and DMSO. This polymer was insoluble in methanol, ethanol, tetrahydrofuran, chloroform, benzene, toluene, ethyl acetate, 1 : 1 mixed solvents of 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-1,2,2,3,3-pentafluoropropane, dimethylformamide, n-hexane, acetone or dichloromethane.

Examples 3 to 7

Each polymer was prepared from monomers and a radical initiator in a similar manner to Example 1. The kinds and molar ratio of the monomers and the radical initiator used in each Example are shown in Table 2.

Table 2

Example	monomer	molar ratio	monomer	molar ratio	radical initiator	molar ratio	CGC (g/L)		
							in H_2O	in DMSO	in DMF
1	GEMA	6	AEM-HCl	12	PFPO-3	2	123	173	n.d.
2	GEMA	6	AEM-HCl	6	PFPO-2	2	267	115	n.d.
3	GEMA	12	AEM-HCl	6	PFPO-2	2	130	49	n.d.
4	GEMA	6.4	AEM-HCl	32	PFPO-2	3.2	n.d.	n.d.	n.d.
5	GEMA	1	AEM-HCl	20	PFPO-3	2	n.d.	n.d.	n.d.
6	GEMA	12	AL-Am-HCl	6	PFPO-2	2	131	90	128
7	NAT	12	AEM-HCl	6	PFPO-2	2	33	32	n.d.

n.d. :not determined,

PFPO-2 : 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoyl peroxide;

PFPO-3: 2,3,3,3-tetrafluoro-2-[1,1,2,3,3,3-hexafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propoxy]propanoyl peroxide;

GEMA : 2-glycosyoxylethyl methacrylate ; AEM-HCl: 2-aminoethyl methacrylate hydrochloride; AL-Am-HCl: allylamine hydrochloride; NAT: N-tris(hydroxymethyl)methylacrylamide; CGC: critical gel concentration

The IR spectrum of the polymers obtained in Examples 3 to 7 are shown in Table 3.

Table 3

Example	IR (KBr)cm^{-1}
3	3442(OH), 3224(NH_3^+), 1710, 1639(C=O), 1310(CF_3), 1245(CF_2).
4	3444(OH), 3160(NH_3^+), 1727, 1623(C=O), 1320(CF_3), 1245(CF_2).
5	3473(OH), 3160(NH_3^+), 1720, 1624(C=O), 1315(CF_3), 1246(CF_2).
6	3442(OH), 3205(NH_3^+), 1715, 1639(C=O), 1340(CF_3), 1245(CF_2).
7	3450(OH), 3147(NH_3^+), 1728, 1649(C=O), 1639(NH_3^+), 1315(CF_3).

Example 8

2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoyl peroxide (PFPO-2, 2.6 mmol) in 1 : 1 mixed solvents of 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-1,2,2,3,3-pentafluoropropane (150 g) was added to an aqueous solution (100 g) of methylcellulose acrylate (MCA: 1.00 g; Monomer-Polymer & Dajac Labs., Inc.) and 2-aminoethyl methacrylate hydrochloride (AEM-HCl: 2.9 mmol). The heterogeneous solution was stirred vigorously at 45 ℃ for 5 hours under nitrogen atmosphere. Methanol was added to the reaction mixture, and the solvent was evaporated. The crude product was reprecipitated from a mixture of methanol and ethyl acetate to give a polymer hydrochloride (0.90 g). IR (KBr): 3463 (OH), 1728 (C=O), 1641 (NH_3^+), 1389(CF_3), 1271 (CF_2) cm^{-1}.

This polymer causes gelation with water, chloroform, DMSO and DMF. The critical gel concentration (CGC) of this polymer in water is 107 g/L.

Examples 9 to 19

Each polymer was prepared from monomers and a radical initiator in a similar manner to Example 8. The kinds and molar ratio of the monomers and the radical initiator used in each Example are shown in Table 4.

Table 4

Example	monomer	molar ratio	monomer	molar ratio	radical initiator	molar ratio	CGC (g/L)		
							in H_2O	in DMSO	in DMF
8	MCA	5	AEM-HCl	3	PFPO-2	3	107	n.d.	n.d.
9	MCA	5	-	-	PFPO-2	1	251	122	116
10	MCA	5	AEM-HCl	15	PFPO-2	3	n.d.	n.d.	n.d.
11	MCA	5	AEM-HCl	15	PFPO-3	3	n.d.	n.d.	n.d.
12	MCA	5	AEM-HCl	20	PFPO-3	3	n.d.	n.d.	n.d.
13	MCA	5	DMAA	13	PFPO-2	1	114	89	81
14	MCA	5	DMAA	13	PFPO-2	3	72	n.d.	n.d.
15	MCA	2.5	DMAA	13	PFPO-2	3	56	n.d.	n.d.
16	MCA	1.2	DMAA	13	PFPO-3	3	68	n.d.	n.d.
17	MCA	4.9	AL-Am-HCl	2.6	PFPO-2	2.6	162	n.d.	n.d.
18	MCA	5	AL-Am-HCl	15	PFPO-3	3	n.d.	n.d.	n.d.
19	MCA	5	AL-Am-HCl	20	PFPO-3	3	n.d.	n.d.	n.d.

n.d. :not determined,

PFPO-2 : 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoyl peroxide;

PFPO-3: 2,3,3,3-tetrafluoro-2-[1,1,2,3,3,3-hexafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propoxy]propanoyl peroxide;

MCA: methylcellulose acrylate; AEM-HCl: 2-aminoethyl methacrylate hydrochloride; DMAA: dimethylacrylamide;

AL-Am-HCl: allylamine hydrochloride; CGC : critical gel concentration

The IR spectrum of the polymers obtained in Examples 10 to 12, 14 and 17 to 19 are shown in Table 5.

Table 5

Example	IR (KBr)cm^{-1}
10	3437(OH), 1724, 1620(C=O), 1310(CF_3), 1240(CF_2).
11	3453(OH), 1725, 1626(C=O), 1320(CF_3), 1244(CF_2).
12	3505(OH), 3116(NH_3^+), 1724, 1628(C=O), 1310(CF_3), 1261(CF_2).
14	3461(OH), 1635(C=O), 1334(CF_3), 1228(CF_2).
17	3469(OH), 1637(C=O), 1322(CF_3), 1240(CF_2).
18	3457(OH), 1638(C=O), 1321(CF_3), 1240(CF_2).
19	3440(OH), 1635(C=O), 1315(CF_3), 1249(CF_2).

Example 20

A 50% aqueous solution of GEMA (5.85 g, 10 mmol) was added to a solution of AEM-HCl (1.66 g, 10 mmol) and 2,2'-azobis(2-amidinopropane) dihydrochloride (V-50, 0.542 g) in water (16.56 g). After adding 100 g of the 1 : 1 mixed solvents of 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-1,2,2,3,3-pentafluoropropane, the mixture was stirred vigorously with a mechanical stirrer at 50℃ for 10 hours under nitrogen atomosphere. The obtained crude product was washed well with methanol to remove the unreacted GEMA and AEM-HCl, and dried in vacuo at 50℃ for 2 days to give a polymer hydrochloride (4.37 g).

IR (KBr): 3440 (NH_3^+, OH), 1718, 1635 (C=O) cm^{-1}.

CGC in water and DMSO are 44 g/L and 19 g/L, respectively.

The obtained polymer causes gelation only with water and DMSO. This polymer was insoluble in methanol, ethanol, tetrahydrofuran, chloroform, benzene, toluene, ethyl acetate, 1 : 1 mixed solvents of 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-1,2,2,3,3-pentafluoropropane, dimethylformamide, n-hexane, acetone or dichloromethane.

Examples 21-158

Each polymer was prepared from monomers and a radical initiator in a similar manner to Example 20. The kinds and molar ratio of the monomers and the radical initiator used in each Example are shown in Table 6.

Table 6

Example No.	monomer	molar ratio	monomer	molar ratio	radical initiator	molar ratio
21	APDAP	13.1	-	-	FBP	4.4
22	APDAP	10.03	-	-	PFPO-2	3.3
23	APDAP	8.4	-	-	PFPO-4	0.8
24	APDAP	10.1	-	-	PFPO-2	0.5
25	APDAP	2.95	-	-	PFPO-4	0.98
26	APDAP	6.16	-	-	PFPO-3	0.62
27	APDAP	11.1	-	-	V-50	1.11
28	VPES	7.3	-	-	PFPO-2	2.6
29	VPES	5.9	MMA	6.3	PFPO-3	1.4
30	APDAA	6	-	-	V-50	2
31	APDAA	10.1	-	-	FBP	3.4
32	APDAA	30.4	-	-	FBP	3.4
33	APDAA	33.1	-	-	FBP	3.3
34	APDAA	66.3	-	-	FBP	3.3
35	APDAA	4.1	-	-	PFPO-4	1.4
36	APDAA	8.9	-	-	PFPO-4	0.89
37	APDAA	17.86	-	-	PFPO-4	0.89
38	APDAA	16.6	-	-	PFPO-3	1.66
39	APDAA	33.1	-	-	PFPO-3	1.66
40	APDAA	4.29	-	-	FBP	2.86
41	APDAA	57.3	-	-	FBP	2.86
42	APDAA	39.0	-	-	FBP	3.9
43	APDAA	4.53	-	-	PFPO-5	0.45
44	APDAA	9.06	-	-	PFPO-5	0.45
45	AEM-HCl	5	-	-	PFPO-2	1

Example No.	monomer	molar ratio	monomer	molar ratio	radical initiator	molar ratio
46	AEM-HCl	5	-	-	CPFP	1
47	AEM-HCl	5	-	-	FBP	1
48	AEM-HCl	5	-	-	PFPO-4	1
49	AEM-HCl	5	-	-	PFPO-3	1
50	HMTP-HCl	60	-	-	CPFP	4
51	VPES	17.51	MMA	18.65	PFPO-2	4.2
52	AEM-HCl	8.3	AMP	24.8	PFPO-2	8.3
53	GEMA	24.9	NM	12.4	PFPO-2	5
54	GEMA	12.1	NM	6.0	PFPO-3	2.4
55	GEMA	25	MAA	25	PFPO-2	5
56	GEMA	20	MAA	20	PFPO-3	4
57	HMTP-HCl	25.1	-	-	PFPO-2	5.0
58	HMTP-HCl	85.86	-	-	PFPO-2	4.29
59	HMTP-HCl	64.4	-	-	PFPO-2	4.29
60	HMTP-HCl	42.2	-	-	PFPO-2	4.2
61	HMTP-HCl	16.59	-	-	V-50	3.3
62	HMTP-HCl	26.87	TVS	8.44	PFPO-2	4.2
63	AHA	41.2	-	-	FBP	4.1
64	AHA	25.1	-	-	PFPO-2	5.0
65	AHA	50.2	-	-	PFPO-2	5.0
66	AHA	26.45	-	-	PFPO-3	2.6
67	NAT	5.3	-	-	PFPO-2	5
68	NAT	28.5	-	-	V-50	2.9
69	NAT	5.3	-	-	PFPO-3	2.6
70	NAT	8	-	-	FBP	4
71	NAT	13	MMA	13	PFPO-3	2.7
72	NAT	21	TVS	21	PFPO-2	4.7
73	NAT	21	TVS	21	FBP	4.4
74	NAT	13	-	-	PFPO-3	2.6
75	HMTP-HCl	4.65	-	-	DPFP	0.31
76	IMA	7	DMAA	93	PFPO-2	1

Example No.	monomer	molar ratio	monomer	molar ratio	radical initiator	molar ratio
77	IMA	7	DMAA	93	PFPO-3	1
78	IMA	13	DMAA	87	V-50	1
79	CQA	11.18	AA	11.18	PFPO-2	3.73
80	CQA	4.28	AA	12.8	PFPO-3	2.14
81	CQA	36.4	DMAA	36.4	PFPO-2	3.64
82	FCAEM	93	DMAA	7	PFPO-2	1
83	FCAEM	7	DMAA	93	PFPO-3	1
84	FCAEM	10	DMAA	90	PFPO-4	1
85	FCAEM	13	DMAA	87	V-50	1
86	HCAEM	1	AM	10	PFPO-3	1
87	HCAEM	2	AM	10	V-50	0.5
88	HCAEM	1	DMAA	10	PFPO-3	1
89	HCAEM	2	DMAA	10	V-50	0.5
90	APB	2.1	-	-	PFPO-2	0.7
91	APB	0.78	DMAA	3.9	PFPO-2	0.78
92	MCA	5	-	-	V-50	1
93	MCA	4.9	DMAA	13	V-50	0.37
94	GEMA	5	AEM-HCl	5	V-50	1
95	GEMA	6	AEM-HCl	3	PFPO-2	1
96	GEMA	2	AL-Am-HCl	1	PFPO-2	2.4
97	GEMA	13	LA	13	PFPO-2	3
98	AL-Am-HCl	9	CDA	28	PFPO-2	9
99	-	-	CDA	28	PFPO-2	9
100	-	-	CDA	30.12	V-50	2.6
101	GEMA	13	CDA	13	PFPO-2	3
102	GEMA	21	AL-Am-HCl	8	PFPO-2	4
103	AM	9	CDA	3	PFPO-2	9
104	NM	14	CDA	14	PFPO-2	3
105	GEMA	6	AL-Am-HCl	20	V-50	3.69
106	GEMA	4	AEM-HCl	20	V-50	3.69
107	GEMA	1	AEM-HCl	10	V-50	1.84

Example No.	monomer	molar ratio	monomer	molar ratio	radical initiator	molar ratio
108	GEMA	0.5	AEM-HCl	10	V-50	1.84
109	MCA	1	AEM-HCl	15	V-50	0.41
110	MCA	2.5	AEM-HCl	15	V-50	0.37
111	MCA	5	AEM-HCl	15	V-50	0.41
112	MCA	7.5	AEM-HCl	15	V-50	0.37
113	MCA	5	AEM-HCl	15	PFPO-2	3
114	MCA	5	AEM-HCl	15	PFPO-3	3
115	MCA	5	AEM-HCl	20	PFPO-3	3
116	MCA	5	AL-Am-HCl	15	V-50	0.41
117	MCA	5	AL-Am-HCl	20	V-50	0.41
118	HMTP-HCl	44.2	GEMA	21.6	PFPO-2	2.2
119	HMTP-HCl	5	AEM-HCl	20	PFPO-2	2.2
120	NAT	10	HMTP-HCl	20	PFPO-2	2.2
121	NAT	2	AEM-HCl	10	PFPO-2	1
122	NAT	1	AEM-HCl	10	PFPO-2	1
123	NAT	2	AEM-HCl	16	PFPO-2	1
124	NAT	1	AEM-HCl	16	PFPO-2	1
125	NAT	3	AEM-HCl	16	PFPO-2	1
126	HA	3.02	AEM-HCl	26.4	PFPO-2	1.5
127	HA	1.5	AEM-HCl	26.8	PFPO-2	1.6
128	HA	1.5	AEM-HCl	26.8	PFPO-2	1.6
129	GEMA	6	AEM-HCl	6	PFPO-2	2
130	GEMA	12	AEM-HCl	6	PFPO-2	2
131	GEMA	6	AEM-HCl	12	PFPO-3	2
132	GEMA	12	AEM-HCl	6	PFPO-2	2
133	GEMA	12	AEM-HCl	6	PFPO-2	2
134	GEMA	12	AEM-HCl	6	PFPO-2	2
135	GEMA	6.4	AEM-HCl	32	PFPO-2	3.2
136	NAT	9.6	AEM-HCl	19.2	PFPO-2	3.2
137	NAT	9.6	AEM-HCl	19.2	PFPO-2	3.2
138	NAT	9.6	AEM-HCl	19.2	PFPO-2	3.2

Example No.	monomer	molar ratio	monomer	molar ratio	radical initiator	molar ratio
139	GEMA	1	AEM-HCl	10	V-50	1.84
140	GEMA	1	AEM-HCl	10	V-50	1.84
141	GEMA	1	AEM-HCl	10	V-50	1.84
142	GEMA	0.5	AEM-HCl	10	V-50	1.84
143	GEMA	0.5	AEM-HCl	10	V-50	1.84
144	GEMA	0.5	AEM-HCl	10	V-50	1.84
145	GEMA	4	AEM-HCl	20	PFPO-3	2
146	NAT	4.8	AEM-HCl	10	PFPO-3	1.6
147	NAT	4.8	AEM-HCl	10	PFPO-3	1.6
148	NAT	4.8	AEM-HCl	10	PFPO-3	1.6
149	MCA	5	DMAA	13	PFPO-2	3
150	MCA	5	DMAA	13	PFPO-2	3
151	MCA	5	DMAA	13	PFPO-2	3
152	MCA	5	AEM-HCl	15	PFPO-3	3
153	MCA	5	AEM-HCl	15	PFPO-3	3
154	MCA	5	AEM-HCl	15	PFPO-3	3
155	MCA	5	AEM-HCl	15	PFPO-3	3
156	MCA	5	AEM-HCl	20	PFPO-3	3
157	MCA	5	AEM-HCl	20	PFPO-3	3
158	MCA	5	AMP	15	PFPO-3	3

PFPO-2 : 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoyl peroxide,

PFPO-3: 2,3,3,3-tetrafluoro-2-[1,1,2,3,3,3-hexafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propoxy]propanoyl peroxide,

V-50: 2,2'-azobis(2-aminopropane)dihydrochloride,

FAP: trifluoroacetyl peroxide,

FBP: 2,2,3,3,4,4,4-heptafluorobutanoyl peroxide,

PFPO-4: 2,3,3,3-tetrafluoro-2-{1,1,2,3,3,3-hexafluoro-2-[1,1,2,3,3,3-hexafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propoxy]propoxy}propanoyl peroxide,

PFPO-5: 2,4,4,5,7,7,8,10,10,11,13,13,14,14,15,15,15-heptadecafluoro-

2,5,8,11-tetrakis(trifluoromethyl)-3,6,9,12-tetraoxapentadecan-1-oyl peroxide,

CPFP: 1,2,2,3,3,4,4,5,5,6,6-undecafluorocyclohexanecarbonyl peroxide,

DPFP: 1,2,2,3,3,4,4,4a,5,5,6,6,7,7,8,8,8a-heptadecafluorodecahydro-1-naphthalenecarbonyl peroxide,

AA: acrylic acid,

AEM-HCl: 2-aminoethyl methacrylate hydrochloride,

AHA: (acryloylamino)(hydroxy)acetic acid,

AL-Am-HCl: allylamine hydrochloride,

AM: 4-acryloylmorpholine,

AMP:2-(acryloylamino)-2-methyl-1-propanesulfonic acid,

APB: 3-(acryloylamino)phenylboronic acid,

APDAA: [[3-(acryloylamino)propyl](dimethyl)ammonio]acetate,

APDAP: 3-[[3-(acryloylamino)propyl](dimethyl)ammonio]-1-propanesulfonate,

CDA: calcium diacrylate,

CQA: 5-chloro-8-quinolinyl acrylate,

DCAEM: 2-{[(2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)carbonyl]amino}ethyl 2-methylacrylate,

DMAA: N,N-dimethylacrylamide,

FCAEM: 2-{[(5-fluoro-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl)carbonyl]amino}ethyl 2-methylaceylate,

GEMA : 2-(glycosyloxyl)ethyl 2-methacrylate ,

HA: N-(hydroxymethyl)acrylamide,

HCAEM: 2-{[(8-hydroxy-5-quinolinyl)carbonyl]amino}-ethyl 2-methylacrylate,

HMTP-HCl: 2-hydroxy-3-(methacryloyloxy)-N,N,N-trimethyl-1-propanaminium chloride,

IMA: 2-[({[2-(1H-imidazol-5-yl)ethyl]amino}carbonyl)amino]ethyl 2-methylacrylate,

LA: lithium acrylate,

MAA: 2-methylacrylic acid,

MMA: methyl 2-methylacrylate,

MCA: methylcellulose acrylate,
NAT: N-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]acrylamide,
NM: 3,6,9,12, 15,18,21,24,27-nonaoxaoctacos-1-yl 2-methylacrylate,
OCAEM: 2-{[(2-oxo-1,2-dihydro-4-pyrimidinyl)carbonyl]amino}ethyl 2-methylacrylate,
TVS: trimethyl(vinyl)silane,
VPES:2-(2-vinyl-1-pyridiniumyl)ethanesulfonate

Preparation 1

The polymer hydrochloride (200mg) obtained in Example 1 and calcium carbonate (21mg) were homogeneously mixed in a mortar. The mixture was put into a test tube to which was added water (0.88 ml) to give a gel. Thus obtained wet gel was dried by using an aspirator and further dried at 50℃ in vacuo for one day to give white gel-powder containing calcium carbonate.

Preparations 2 to 7

Each polymer hydrochloride (200mg) obtained in Examples 2, 3, 4, 5, 11 and 14 was treated in a similar manner to Preparation 1 to give white gel-powder containing calcium carbonate.

Preparation 8

A 1% calcium chloride aqueous solution (2.29 ml) was added to the polymer hydrochloride (105 mg) obtained in Example 7 in a test tube to give a gel. Thus obtained gel was dried in a similar manner to Preparation 1 to give white gel-powder containing calcium chloride.

Preparations 9 and 10

Each polymer hydrochloride (105 mg) obtained in Examples 14 and 15 was treated in a similar manner to Preparation 8 to give a white gel-powder containing calcium chloride.

Preparation 11

A 2.5 % calcium chloride aqueous solution (2.29 ml) was added

to the polymer hydrochloride (105 mg) obtained in Example 7 to give a gel. Thus obtained gel was dried in a similar manner to Preparation 1 to give white gel-powder containing calcium chloride.

Preparation 12

The polymer hydrochloride (105 mg) obtained in Example 14 was treated in a similar manner to Preparation 11 to give white gel-powder containing calcium chloride.

Preparation 13

A 5 % calcium chloride aqueous solution (2.29 ml) was added to the polymer hydrochloride (105 mg) obtained in Example 7 to give a gel. Thus obtained gel was dried in a similar manner to Preparation 1 to give white gel-powder containing calcium chloride.

Preparations 14 to 16

Each polymer hydrochloride (105 mg) obtained in Example 11, 12 and 14 was treated in a similar manner to Preparation 13 to give white gel-powder containing calcium chloride.

Preparation 17

A 10 % calcium chloride aqueous solution (2.29 ml) was added to the polymer hydrochloride (105 mg) obtained in Example 14 to give a gel. Thus obtained gel was dried in a similar manner to Preparation 1 to give white gel powder containing calcium chloride.

The CGC values in water of the gel-powder obtained in some of the above Preparations are shown in the following Table 7.

Table 7

Preparation	CGC (g/L)	Preparation	CGC (g/L)
1	142.06	10	115
2	71.64	12	233
3	71.68	14	295
4	227.61	15	217
5	274.38	16	102
9	256	17	175

Preparations 18-40

Each preparation was obtained from the polymer and a calcium compound in a similar manner to Preparations 1 to 17. The kinds and molar ratio of the polymer and the calcium compound are shown in Table 8.

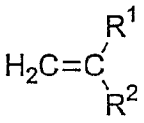
Table 8

Preparation No.	polymer obtained in Example	calcium compound	molar ratio of calcium compound with respect to the polymer
18	132	$CaCl_2$	1%
19	133	$CaCl_2$	2.5%
20	134	$CaCl_2$	5%
21	136	$CaCl_2$	1%
22	137	$CaCl_2$	2.5%
23	138	$CaCl_2$	5%
24	139	$CaCl_2$	1%
25	140	$CaCl_2$	2.5%
26	141	$CaCl_2$	1.84%
27	142	$CaCl_2$	1.84%
28	143	$CaCl_2$	1.84%
29	144	$CaCl_2$	1.84%
30	145	$CaCO_3$	2%

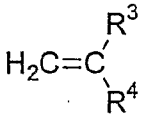
Preparation No.	polymer obtained in Example	calcium compound	molar ratio of calcium compound with respect to the polymer
31	146	$CaCl_2$	1%
32	147	$CaCl_2$	2.5%
33	148	$CaCl_2$	5%
34	150	$CaCl_2$	5%
35	151	$CaCl_2$	10%
36	153	$CaCl_2$	1%
37	154	$CaCl_2$	2.5%
38	155	$CaCl_2$	5%
39	156	$CaCl_2$	2.5%
40	157	$CaCl_2$	5%

CLAIMS

1. A polymer or its salt which is obtainable by polymerization of a monomer of the formula (I) or its salt in the presence of a radical initiator, or by polymerization of a monomer of the formula (I) or its salt with a monomer of the formula (II) or its salt in a molar ratio of (I) : (II) being 1:0.1 to 1:25 in the presence of a radical initiator



(I)



(II)

wherein

R^1 and R^3 are each hydrogen atom or lower alkyl group,

R^2 and R^4 are each acyl group,

aliphatic silyl group,

amino lower alkyl group which may have one or more suitable substituent(s),

heterocyclic group which may have one or more suitable substituent(s) or

carboxy group esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl.

2. The polymer or its salt of Claim 1, wherein the acyl groups for R^2 and R^4 are each

lower alkyl carbamoyl group, aryl carbamoyl group, lower alkoxycarbonyl group, heterocyclicoxycarbonyl group or heterocyclccarbonyl group, each of which may have one or more suitable substituent(s) or

tri(lower)alkylsilyl group.

3. The polymer or its salt of Claim 1, wherein the acyl groups for R^2 and R^4 are each

lower alkyl carbamoyl group which may have one or more substituents selected from the group consisting of sulfo, hydroxy, carboxy, amino, sulfo(lower)alkylamino and carboxy(lower)alkylamino, or

lower alkoxycarbonyl group which may have one or more substituents selected from the group consisting of hydroxy, amino, lower alkylamino, glycosyloxy, heterocyclic carbonylamino and heterocyclic(lower)alkylaminocarbonylamino.

4. The polymer or its salt of Claim 1, wherein the acyl groups for R^2 and R^4 are each

lower alkyl carbamoyl group which may be substituted with one or more hydroxy, or

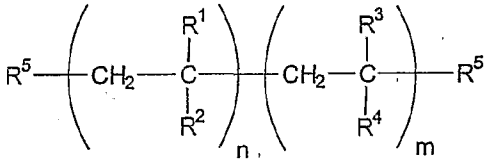
lower alkoxycarbonyl group substituted with amino or glycosyloxy.

5. The polymer or its salt of Claim 1, wherein the radical initiator is represented by the formula (III):

$$(R^5COO)_2 \qquad \text{(III)}$$

wherein R^5 is a perfluoro(lower)alkyl group which may have one or more suitable substituent(s) or a cycloalkyl group substituted with one or more fluorine atom(s).

6. The polymer or its salt of Claim 5, which is represented by the formula (IV):



(IV)

wherein R^1 and R^3 are each hydrogen atom or lower alkyl group,

R^2 and R^4 are each acyl group,

aliphatic silyl group,

amino lower alkyl group which may have one or more suitable substituent(s),

heterocyclic group which may have one or more suitable

substituent(s) or

carboxy group which may be esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl and

R^2 and/or R^4 may be intramolecularly and/or intermolecularly crosslinked with another R^2 or R^4,

R^5 is a perfluoro(lower)alkyl group which may have one or more suitable substituent(s) or a cycloalkyl group substituted with one or more of fluorine atom(s),

n is an integer of 1 or more, and

m is an integer of 0, 1 or more.

7. The polymer or its salt of Claim 6, wherein R^2 and R^4 are each lower alkyl carbamoyl group or lower alkoxycarbonyl group, each of which may have one or more suitable substituent(s),

amino lower alkyl group or

carboxy group which may be esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl, and

R^2 and/or R^4 may be intramolecularly and/or intermolecularly crosslinked with another R^2 or R^4.

8. The polymer or its salt of Claim 7, wherein R^2 and R^4 are each lower alkyl carbamoyl group which may have one or more hydroxy, lower alkoxycarbonyl group substituted with amino or glycosyloxy, amino lower alkyl group or

carboxy group esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl, and

R^2 and/or R^4 may be intramolecularly and/or intermolecularly crosslinked with another R^2 or R^4.

9. The polymer or its salt of Claim 8, which is obtainable by polymerization of 2-glucosylethyl methacrylate (GEMA) with 2-aminoethyl methacrylate hydrochloride (AEM-HCl) in the presence of 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoyl

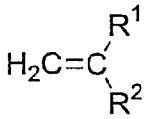
peroxide (PFPO-2) in the molar ratio of GEMA : AEM-HCl being 1:2, 1:1, 1:0.5, 1:5 or 1:20,
polymerization of GEMA with allylamine hydrochloride (AL-Am-HCl) in the presence of PFPO-2 in the molar ratio of GEMA:AL-Am-HCl being 1:0.5,
polymerization of N-tris(hydroxymethyl)methylacrylamide (NAT) with AEM-HCl in the presence of PFPO-2 in the molar ratio of NAT:AEM-HCl being 1:0.5,
polymerization of methylcellulose acrylate (MCA) in the presence of PFPO-2,
polymerization of MCA with AEM-HCl in the presence of PFPO-2 in the molar ratio of MCA:AEM-HCl being 1:0.6 or 1:3,
polymerization of MCA with AEM-HCl in the presence of PFPO-3 in the molar ratio of MCA:AEM-HCl being 1:3 or 1:4,
polymerization of MCA with dimethylacrylamide (DMAA) in the presence of PFPO-2 in the molar ratio of MCA:DMAA being 1:2.6 or 1: 5.2,
polymerization of MCA with DMAA in the presence of PFPO-3 in the molar ratio of MCA:DMAA being 1:10.83,
polymerization of MCA with AL-Am-HCl in the presence of PFPO-2 in the molar ratio of MCA:AL-Am-HCl being 1:1.88 or 1:3, or
polymerization of MCA with AL-Am-HCl in the presence of PFPO-3 in the molar ratio of MCA:AL-Am-HCl being 1:4.

10. The polymer or its salt of Claim 1, wherein the radical initiator is the one having azo group.

11. The polymer or its salt of Claim 10, wherein
R^2 and R^4 are each
lower alkyl carbamoyl group which may have one or more suitable substituent(s),
lower alkoxy group may have one or more suitable substituent(s),
heterocyclic carbonyl group,
amino lower alkyl group which may have one or more suitable substituent(s), or
carboxy group which may be esterified by the residue of cellulose

optionally substituted with one or more lower alkyl and/or lower alkenoyl.

12. A polymer or its salt which is obtainable by polymerization of a monomer of the formula (I) or its salt in the presence of a radical initiator,

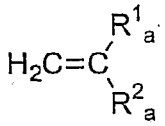


(I)

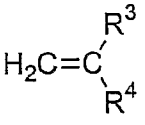
R^1 is hydrogen atom or lower alkyl group,

R^2 is lower alkyl carbamoyl group optionally substituted with one or more substituents selected from the group consisting of hydroxy, carboxy, sulfo, N,N-di(lower)alkyl-N-sulfonato(lower)alkylammonio and N,N-di(lower)alkyl-N-carboxylato(lower)alkylammonio;
aryl group optionally substituted with dihydroxyboranyl;
lower alkoxy carbonyl group substituted with one or more substituents selected from hydroxy, ammonio and tri(lower)alkylammonio;
carboxy group esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl;
or
pyridinium group substituted with sulfonato(lower)alkyl,

or by polymerization of a monomer of the formula (Ia) or its salt with a monomer of the formula (II) or its salt in a molar ratio of (Ia) : (II) being 1:0.1 to 1:25 in the presence of a radical initiator



(Ia)



(II)

wherein R^1_a is hydrogen atom or lower alkyl group,

R^2_a is lower alkyl carbamoyl group;
lower alkoxy carbonyl group substituted with optionally substituted-heterocycliccarboamido,
heterocyclic(lower)alkylureido or glycosyloxy; or
heterocyclicoxycarbonyl group optionally substituted with

halogen or hydroxy;

R^3 is hydrogen atom or lower alkyl group,

R^4 is lower alkyl carbamoyl group optionally substituted with sulfonato;

lower alkoxycarbonyl group optionally substituted with lower alkoxy in which the alkyl moiety may be interrupted by oxygen atom(s);

carboxy group which may be esterified by the residue of cellulose optionally substituted with one or more lower alkyl and/or lower alkenoyl;

amino(lower)alkyl group;

heterocyclic carbonyl group; or

tri(lower)alkylsilyl group,

provided that when $R^2{}_a$ and R^4 are the same, then $R^1{}_a$ and R^3 are different from each other.

13. A pharmaceutical composition comprising a polymer or its salt of any one of Claims 1 to 12, as an active ingredient, in association with a pharmaceutically acceptable, non-toxic carrier or excipient.

14. A polymer or its salt of any one of Claims 1 to 12 for use as a medicament.

15. Use of a polymer or its salt of any one of Claims 1 to 12 for manufacture of a medicament for treatment and/or prevention of hyperphosphoremia.

16. A method for the treatment and/or prevention of hyperphosphoremia, by administering an effective amount of a polymer or its salt of any one of Claims 1 to 12 to a patient suffering from hyperphosphoremia.